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THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE MECHANISM OF GASTROESOPHAGEAL REFLUX DISEASE DEVELOPMENT IN PATIENTS WITH ISCHEMIC HEART DISEASE

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SUMMARY – Ischemic heart disease (IHD) and gastroesophageal reflux disease (GERD) are among the most common diseases worldwide, which in a considerable percentage of cases occur together, thus complicating symptoms, posing problems for timely diagnosis and hindering development of a comprehensive treatment regimen for both diseases. Research has shown that endothelial dysfunction is one of the major pathophysiological mechanisms in the development of IHD. Endothelial dysfunction also affects regional perfusion of the esophagus, thus compromising esophageal tissue defense mechanisms. The aim of our study was to investigate the role of endothelial dysfunction in the mechanisms of GERD development in patients with IHD. For the purpose of this study, we collected data on serum levels of endothelin-1, nitric oxide metabolites and lipid peroxidation products, gastric pH, parameters of regional blood flow, and quality of life assessment. Study results revealed that in IHD patients with concomitant GERD, endothelial dysfunction manifested by a significant increase in the levels of endothelin-1 and lipid peroxidation products, with decreased levels of nitric oxide metabolites, regional blood flow and quality of life. These findings suggest that hypoxia of the esophageal mucosa, caused by endothelial dysfunction, leads to a decrease in the esophageal tissue resistance and to esophageal lower sphincter dysfunction, which, in turn, are the leading factors in the development of GERD.

Key words: *Myocardial ischemia; Gastroesophageal reflux; Endothelin-1; Nitric oxide; Lipid peroxidation; Regional blood flow; Quality of life; Hypoxia; Esophageal sphincter, lower*

Introduction

Ischemic heart disease (IHD) continues to be one of the most common diseases worldwide[1,2]. In recent years, there has been an increasing trend in the incidence of the disease in younger people and in clinical comorbidity. One of the leading places in comorbid pathology belongs to gastroesophageal reflux disease (GERD)[1,3]. Research data suggest that more than one-third of patients with coronary heart disease suffer from reflux esophagitis of varying severity while more than 60% of non-cardiac chest pain episodes in patients with IHD are associated with GERD[3,4]. The concurrent presence of these diseases modifies symptoms, aggravates clinical presentation and jeopardizes the timeliness of the correct diagnosis[2,3]. A number of factors and mechanisms contribute to the development of such comorbidity. Shared afferent vagal innervation of the esophagus and the heart is responsible for similarity in clinical presentations of esophageal and cardiac chest pain. Vagal innervation is also the underlying mechanism for cardiac arrhythmia and ischemia being triggered by esophageal irritation with

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acidic refluxate, as well as esophageal spasm being triggered by cardiac ischemia[4,5]. Several studies have shown that development of GERD symptoms is caused by the use of aspirin, calcium channel blockers and nitrates, medications commonly used for IHD[6,7]. Nitrates decrease lower esophageal sphincter pressure, calcium channel blockers affect esophageal motility slowing peristalsis, and aspirin is an esophageal and gastric mucosa irritant. All these drug-related mechanisms contribute to the development of GERD in patients with IHD. Substantial research data suggest that endothelial dysfunction is the leading mechanism in the pathogenesis of IHD. With regard to the esophagus, endothelial dysfunction affects regional blood circulation causing tissue hypoxia, thus decreasing esophageal tissue resistance and its ability to withstand acidic refluxate[8-11].

Based on this, the purpose of the present study was to investigate the role of endothelial dysfunction in the mechanisms of development of GERD in patients with IHD.

Subjects and Methods

The present study was conducted in a total of 105 adult subjects divided into three groups. Group 1 included 45 adults (30 women and 15 men) aged 35 to 45 years with angina pectoris I-II functional class comorbid with non-erosive form of GERD. The diagnosis of IHD was based on ICD-10 classification, while the diagnosis of GERD was based on ICD-10 and the Montreal Consensus 2006 recommendations. Patients with other comorbidities such as obesity, insulin resistance, diabetes, chronic obstructive pulmonary disease, and coronary syndrome were not included in the study group. Group 2 consisted of 40 adults (26 women and 14 men) aged 33 to 44 years with non-erosive form of GERD without comorbidity. Control group consisted of 20 healthy individuals of both sexes aged 33 to 44 years. The study was conducted at clinical sites of the Department of Therapy, Rheumatology and Clinical Pharmacology, Kharkiv Medical Academy of Postgraduate Education. The study was approved by the institutional Ethics Committee of the Kharkiv Medical Academy of Postgraduate Education and by administrations of the clinical sites. A written informed consent was obtained from all study participants.

Endothelial function assessment was performed by measurement of serum levels of endothelin-1, nitric oxide (NO) metabolites and lipid peroxidation products. Endothelin-1 level was measured using commercially available Endothelin-1 ELISA System kit, according to the manufacturer's protocol (Amersham Pharmacia Biotech, UK). Levels of stable NO metabolites (NO2 blood and NO2 + NO3 blood) was determined by spectrometry (Griess-Ilosvaya method). Quantification of the lipid peroxidation products was performed by measuring levels of serum thiobarbituric acid-reactive substances (TBARS) using a commercially available ELISA kit, according to the manufacturer's protocol (HBO REAKOMPLEKS, Russia).

Gastric secretory function was assessed by endogastric pH-metry with ML-2 unit (production of Ukraine).

The 12-lead baseline electrocardiography (ECG) was performed according to standard procedures on the UCARD-200 unit (production of Russia).

The state of the regional blood circulation was assessed by measurement of blood flow velocity and celiac trunk diameter. These parameters were determined using sonography with color Doppler mapping performed on an Aloka-SSD-650 ultrasound apparatus (production of Japan).

Patient quality of life was assessed by using the SF-36 questionnaire.

Statistical data processing was carried out by the methods of variation and parametric statistics for biomedical research using Excel for Windows and Statistica 6.0 software.

Results and Discussion

The mean values of endothelin-1 levels were as follows: 8.3±0.57 pmol/L in group 1 patients (IHD + GERD) and 4.1±0.23 pmol/L in group 2 patients (GERD), indicating significant increase in comparison with normal values of 1.92±0.23 pmol/L. The levels of endothelin-1 in control group were within the normal limits.

The mean levels of stable NO metabolites were as follows: group 1, NO2 1.33±0.5 μmol/L and NO2+NO3 19.78±2.77 μmol/L; group 2, NO2 1.9±0.20 μmol/L and NO3+NO2 25.41±9.85 μmol /L. The results were indicative of significant decrease in the levels of stable NO metabolites when compared

with normal values (NO2 2.8±0.22 μmol/L and NO2+NO3 31.50±3.05 μmol/L) and those recorded in control group.

There were apparent differences in the results between the study groups. Group 1 patients had a statistically significant ($p<0.001$) increase in endothelin-1 levels and decrease in the levels of stable NO metabolites as compared with group 2 and control group. Group 2 patients showed a statistically significant increase in the levels of endothelin-1 and decrease in the levels of stable NO metabolites compared with control group, but deviation from the normal values was significantly lower than in group 1 patients. Furthermore, in group 1, deviation from the normal levels of endothelin-1 (increase) was more pronounced than changes in the levels of NO metabolites (decrease), while deviations from the normal levels of those biomarkers in group 2 patients were comparable.

The mean level of TBARS was 11.81±0.62 μmol /L in group 1 and 15.25±0.74 μmol/L in group 2, indicating significant increase as compared with normal levels of 4.5±0.35 μmol/L. On group comparison, group 2 patients had significantly higher levels of lipid peroxidation products than both group 1 and control group.

Assessment of the regional blood circulation revealed a statistically significant reduction in the celiac trunk diameter and decrease in blood flow velocity in the celiac trunk in both groups 1 and 2 as compared with normal values of 0.99±0.14 cm for celiac trunk diameter and 14.4±0.9 cm/s for blood flow velocity. The mean values of celiac trunk diameter were 0.7±0.1 cm in group 1 and 0.88±0.12 cm in group 2. The mean blood flow velocity measured 7.8±0.5 cm/s in group 1 and 10.3±0.6 cm/s in group 2. In group 1 patients, decrease in the celiac trunk diameter prevailed over decrease in blood flow velocity in its significance. Group comparison showed the decrease in the values of celiac trunk diameter and blood flow velocity in group 2 patients to be apparent in comparison with control group, but less significant than in group 1 patients.

Gastric pH was measured in the body of the stomach, with pH 1.7±0.2 being considered a normal value. The mean value of gastric pH was 1.3±0.1 in group 1 and 1.1±0.1 in group 2. Such a decrease in pH values indicated increase in gastric acidity, which was significantly greater in group 2 patients in comparison with both the control group and group 1 patients.

The study revealed a significant decrease in the quality of life indicators in all main domains of the SF-36 scale for both patient groups as compared with the control group ($p<0.001$). Moreover, in patients with IHD and concomitant GERD, severe decline was recorded in the general health and social functioning scales, which amounted to 42.3±4.5 points and 51.2±4.4 points, respectively (normal, 77.8±5.1 points and 85.3±4.6 points, respectively). At the same time, in patients with GERD without comorbidity, the scores were 55.9±3.7 and 68.2±3.3 points, respectively. Thus, according to the results, the indicators were significantly higher in group 2 than in control group ($p<0.001$), but significantly lower than in group 1. At the same time, the indicators of pain intensity scales, role and physical functioning were significantly higher in group 2, with the mean values of 35.4±3.7 and 33.2±2.8 points, respectively (normal, 75.7±4.2; 73.8±3.2 points) as compared with control group and group 1 (48.4±4.5; 49.7±3.8 points).

In both patient groups, there was strong correlation (group 1, $r=0.76$; group 2, $r=0.70$) between the quality of life scores and study variables, i.e. levels of endothelin-1, NO metabolites, lipid peroxidation products, parameters of regional blood flow, and gastric pH. Study results suggest that endothelial dysfunction plays one of the leading roles in the development of GERD in IHD patients. Endothelial dysfunction is evidenced by a significant increase in the levels of endothelin-1 and decrease in the levels of NO metabolites and parameters of regional blood flow in celiac trunk, which reduces esophageal tissue resistance and results in the lower esophageal sphincter dysfunction. In GERD patients without concomitant pathology, stress evidenced by increase in the quality of life indicators (intensity of pain, role and physical functioning) triggers an increased production of hydrochloric acid in the stomach and elevation of endothelin-1 levels. This, in turn, leads to a decrease in regional blood flow and tissue hypoxia, resulting in higher rates of lipid peroxidation products, and reduced esophageal tone and motility, and helps maintain the increased production of hydrochloric acid. It may be extrapolated that endothelial dysfunction is one of the major mechanisms that triggers the development of GERD in IHD patients. Besides, in patients with isolated GERD, endothelial dysfunction can develop as a sec-

ondary pathology, aggravating the clinical course of the disease. The study findings suggest that in IHD patients with concomitant GERD, the anti-reflux barrier dysfunction at the esophagogastric junction occurs due to reduced esophageal tissue defense mechanisms resulting from perfusion-related tissue hypoxia, whereas in GERD patients without comorbidity, anti-reflux barrier dysfunction is induced by the increased corrosive properties of refluxate. Study results pointed to the need for a differentiated approach to treatment based on the specific role endothelial dysfunction plays in the pathophysiology of both diseases.

Conclusions

1. Patients with IHD and concomitant GERD have a significant decrease in the quality of life parameters on all scales compared with control group, and in the general health and social functioning indicators, significantly higher than in GERD patients without comorbidity. In patients with isolated GERD, the study demonstrated a significant increase in pain, physical functioning and role-playing indicators compared with normal values and group 1 patients.
2. Patients with IHD and concomitant GERD showed a statistically significant increase in endothelin-1 levels and decrease in the levels of stable NO metabolites as compared with GERD patients without comorbidity and control group.
3. Patients with GERD without comorbidity had distinct reduction in the values of celiac trunk diameter and blood flow velocity in comparison with control group, but less significant than in IHD patients with concomitant GERD.
4. Increase in the levels of lipid peroxidation products and increased gastric juice acidity in IHD patients with concomitant GERD was apparent as compared with control group, but less significant than in GERD patients without comorbidity.
5. The findings suggest that endothelial dysfunction in IHD patients with concomitant GERD affects esophageal tissue defense mechanisms precipitating anti-reflux barrier dysfunction at the esophagogastric junction, while in GERD patients without comorbidity it potentiates corrosive properties of refluxate.

Results of the study will contribute to more extensive detection of endothelial dysfunction in patients with IHD accompanied by GERD. In addition, these results will be used to develop methods for preventing development of GERD in patients with IHD.

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Sažetak

ULOGA ENDOTELNE DISFUNKCIJE U MEHANIZMU NASTANKA GASTROEZOFAGUSNE REFLUKSNE BOLESTI KOD BOLESNIKA S KORONARNOM BOLESTI SRCA

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Danas su koronarna bolest srca (KBS) i gastroezofagusna refluksna bolest (GERD) među najčešćim bolestima u svijetu koje se u značajnom postotku slučajeva javljaju komorbidno pri čemu znatno otežavaju kliničku sliku i razvoj sveobuhvatne sheme terapije za obje bolesti. S obzirom na to da poremećaj funkcije endotela igra važnu ulogu u nastanku KBS, kao i u održavanju rezistentnosti tkiva jednjaka, cilj našega istraživanja bio je procijeniti ulogu endotelne disfunkcije u mehanizmu nastanka GERB kod bolesnika s KBS. Polazeći od postavljenog cilja mjerili smo serumske razine endotelina-1, metabolite dušikova oksida i produkata peroksidacije lipida, želučani pH, parametre regionalnog protoka krvi te kvalitetu života bolesnika. Rezultati su pokazali da se endotelna disfunkcija u bolesnika s IHD i GERD očituje povišenim razinama endotelina-1 i produkata peroksidacije lipida, uz snižene razine metabolita dušikova oksida, regionalnog protoka krvi i kvalitete života. Ovi nalazi ukazuju na to da hipoksija ezofagusne sluznice uzrokovana endotelnom disfunkcijom dovodi do smanjenja otpornosti ezofagusnog tkiva i disfunkcije donjeg ezofagusnog sfinktera, a to su vodeći čimbenici razvoja GERD.

Ključne riječi: *Miokard, ishemija; Gastroezofagusni refluks; Endotelin-1; Dušični oksid; Lipidna peroksidacija; Regionalni optok krvi; Kvaliteta života; Hipoksija; Ezofagusni sfinkter, donji*